Title: Effects of deep-brain stimulation of the subthalamic nucleus on freezing of gait in Parkinson's disease: a prospective controlled study.

Subtitle: STN-DBS effects on FOG

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ABSTRACT

Background: Freezing of gait (FOG) is a debilitating gait disorder in Parkinson's disease (PD) with partial responsiveness to dopaminergic medication. To date, notions about the effects of subthalamic deep brain stimulation (STN-DBS) on FOG remain controversial.

Objectives: To compare the effects of bilateral STN-DBS and continued best medical treatment (BMT) on FOG occurrence, FOG severity and clinical outcomes in PD patients at 6 and 12 months follow-up.

Methods: In this prospective, controlled study, 41 PD patients with at least 5 years disease duration participated. Twenty-four subjects (20 with FOG) were treated with STN-DBS and 17 (15 with FOG) continued BMT. The primary outcome was the New Freezing of Gait Questionnaire (NFOGQ) at 6 months post-surgery. Other outcomes were the NFOGQ at 12 months and clinical outcomes (UPDRS III, timed gait, falls and quality of life) at both time points.

Results: STN-DBS increased the likelihood to convert from being a freezer to a non-freezer at 6 and 12 months follow-up (RRR=0.4). However, 45% of baseline freezers still experienced FOG 6 and 12 months post-surgery albeit with reduced severity. Three baseline non-freezers (1/2 BMT-treated, 2/4 STN-DBS-treated) developed FOG during follow-up. STN-DBS-induced benefits on FOG were mostly mediated by baseline levodopa equivalent dose, altered medication-intake and reduced motor fluctuations.

Conclusions: In contrast to continued BMT, STN-DBS reduced FOG occurrence and severity at 6 months post-surgery with largely sustained effects at 12 months follow-up. Longer follow-up periods are needed to test whether FOG improvements after STN-DBS persist with disease progression.

INTRODUCTION

Freezing of gait (FOG) is a common, debilitating symptom occurring mostly in the mid to later stages of Parkinson's disease (PD) and other parkinsonian syndromes.[1] The responsiveness of FOG to dopaminergic therapy varies between PD patients.[1, 2] FOG manifests itself mostly during *off*-periods but can also occur in *on*-periods.[1] Occasionally, pure *on*-FOG occurs only when the levodopa dose is increased.[2] High frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) is the most commonly applied surgical treatment in PD patients with levodopa-induced motor complications and dyskinesias.[3] Although the biophysical basis is incompletely understood, STN-DBS is thought to normalize pathological patterns of basal ganglia activity affecting thalamocortical and brainstem circuitries.[4, 5] STN-DBS improves Parkinsonian motor symptoms and quality of life, allowing a reduction in dopaminergic medication and thus reducing levodopa-induced complications.[6, 7]

To date, the potentially beneficial effects of STN stimulation on FOG are less clear for three main reasons. First, laboratory assessment of FOG on and off stimulation is problematic due to its unpredictable nature and may not reflect FOG in daily life.[1] Second, both improvement and worsening of FOG have been reported depending on voltage/frequency stimulation settings and follow-up time.[8-11] Third, STN-DBS effects on FOG have never been compared with continued best medical treatment (BMT) in a controlled design.

This study aimed to compare the effects of bilateral STN stimulation and continued BMT on FOG occurrence in PD patients after 6 and 12 months. Additionally, we compared the effect of STN-DBS and continued BMT on FOG severity and disease-related clinical parameters.

PATIENTS AND METHODS

Participants. Participants were recruited in the Movement Disorders Clinic of the University Hospitals Leuven. All PD patients who were considered eligible for STN stimulation between March 1, 2007 and April 1, 2010, were invited to participate. The inclusion criteria were: 1) PD diagnosis;[12] 2) disease duration ≥ five years; 3) a combination of disabling motor fluctuations and dyskinesias or disabling medication-resistant tremor. The presence of FOG was not an inclusion criterion. Both freezers and non-freezers were included in order to capture spontaneous or STN-DBS-induced development of FOG.[11] Patients were excluded if they 1) had a mini mental state examination (MMSE) score < 24/30; 2) had severe psychiatric problems; 3) were older than 70 years. Informed consent was obtained. Participation in the study entailed that the patient could freely choose between undergoing DBS and continuing BMT and in both cases agreed to undergo a standardized clinical evaluation at baseline and 6 and 12 months later. Continued BMT denoted the use of pharmacological compounds, mostly levodopa, aimed at prolonging clinical *on* periods.[1, 2] Both in the DBS and BMT group, adjustments of medication were allowed during the study if judged necessary by the treating neurologist (W.V.).

Standard protocol approvals, registrations, and patient consents. Participants gave informed consent consistent with the Declaration of Helsinki. Ethics approval was received by the Commissie Medische Ethiek KULeuven.

Study design and procedures. The design was a prospective, controlled cohort study with a consecutive inclusion. Patients were evaluated at baseline (just prior to surgery in the STN-group) and 6 and 12 months later. At each time point, we evaluated the occurrence and severity of FOG by means of the New Freezing of Gait Questionnaire (NFOG-Q),[13] using a FOG verification video. The NFOG-Q consists of 3 parts: Part I (item 1) assesses whether patients had experienced FOG during the past month during their *on* and/or *off* stage; Part II (items 2-6) evaluates the frequency and duration of FOG episodes in general as well as during

turning and gait initiation separately; 3) Part II (items 7-9) quantifies the impact of FOG on patients' quality of life. The primary outcome was the occurrence of FOG (0/1 score on item 1 of the NFOG-Q) at 6 months follow-up, irrespective of whether it occurred *on* or *off* medication. FOG occurrence after 12 months served as secondary outcome. The tertiary outcome was FOG severity in those who reported FOG, assessed by Part II and III of the NFOG-Q. Other clinical outcomes were: the Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor examinations) and part IV (treatment complications), the Parkinson's Disease Questionnaire-39 (PDQ-39) (quality of life,[14]), the timed get up & go test (TUG,[15]) and fall occurrence during the previous three months (score 0= never, 1= once, 2= twice or more). Cognitive impairment was measured using the MMSE. Descriptive variables included age, gender, disease duration, Levodopa Equivalent Dose (LED) and Hoehn and Yahr stage. All evaluations were performed *on* medication and *on* stimulation (in the intervention group), reflecting the patients' status in daily life.

Operation and DBS parameters. All patients in the STN-group underwent DBS implantation by the same neurosurgeon. Patients were *off* medication for at least 24 hours before operation. First the bilateral implantation of a quadripolar electrode (3389, Medtronic Inc) in STN was carried out, followed by the implantation of a pulse generator (Kinetra or Activa PC, Medtronic Inc.). The stimulator was inserted immediately after electrode implantation, or 1 week after stereotactic intervention. Stereotactic localisation of the electrodes in the motor part of the STN was determined by MRI, micro-electrode mapping and electrical stimulation in the awake patient, using CRW frame (Radionics), Framelink (Medtronic Inc.) and microdrive for 5 micro-electrodes (Ben's gun). The final electrode location was evaluated with postoperative imaging (MRI or CT, fused with preoperative MRI). Postoperatively, optimal stimulation parameters were determined considering symptoms and side effects. Six months after surgery, most patients were treated with

monopolar stimulation (n = 19/24, 79.2%), 60µsec pulse width (n=19/24, 79.2%) and 130 Hz stimulation frequency (n=20/24, 83.3%). The mean voltage was 2.5 V, (range 1.1-5.0 V). Stimulation settings were largely similar at 12 month follow up.

Statistical analysis. Data normality was checked using Kolmogorov-Smirnov tests. Baseline group differences were studied using Chi-square (X^2) statistics, Fisher's Exact tests, Wilcoxon rank sum tests or unpaired t-tests, as appropriate. Group differences in FOG occurrence and severity at six months were examined using Fisher's Exact statistics and unpaired t-tests. The Cohen effect size, number needed to treat (NNT) and relative risk reduction (RRR) for FOG occurrence were determined. Other clinical outcomes with normal distributions were compared between groups and time moments using a mixed repeated measures ANOVA model. Wilcoxon rank sum between-group comparisons and Friedman within-group analysis were applied for not normally distributed clinical variables.

Generalized Estimating Equations (GEE) models were used to evaluate FOG occurrence over time in both groups while controlling for confounders with a post-hoc sequential Bonferroni correction for all pairwise comparisons.[16] Main effects of group and time and their interaction effect were consecutively entered into the model. The quasi likelihood under independence criterion (QIC), an estimate of goodness of fit, proved always better with the interaction effect included. We used a Wald X^2 statistic to investigate the significance of the interaction in the GEE model. As the GEE model excludes missing variables, missing data points were imputed using the last observation carried forward (LOCF) yielding a worst case approach. Intention-to-treat analysis served to investigate whether the results were influenced by dropout. GEE statistics with a normal distribution model were used to analyse FOG severity. Exploratory analysis were conducted to understand the relation between STN-DBS induced conversion from being a freezer to a non-freezer on the one hand and change in clinical variables on the other hand using Rank Biserial correlations for binary outcomes

(conversion yes/no) in STN-DBS-treated baseline freezers. If appropriate, a multivariate analysis was applied next. Statistical analyses were performed using SPSS, version 16. P values < 0.05 were considered significant.

RESULTS

Baseline characteristics. Of the 42 invited patients, one declined to take part in the study. Twenty-four patients decided to undergo bilateral STN stimulation and 17 chose to continue on BMT. One baseline freezer in the STN-group was lost to follow-up at 6 months, but evaluated at 12 months. Five persons in the BMT group, who had FOG at 6 months, were lost at 12 months because an STN stimulator (n = 3) or a levodopa/carbidopa enteral infusion system (n = 2) was implanted (See Supplement 1 for a flowchart of the study).

Table 1 shows that STN- and BMT-groups had comparable demographic and clinical profiles at baseline, except for LED which was higher in STN- (median = 1113 mg/day) than BMT-patients (median = 680 mg/day, p=0.0009). There were no group differences in the dose of MAO-B inhibitors, amantadine and anticholinergic (N=1) medication (See Supplement 2). None of the patients were treated with methylphenidate. There were no baseline group differences regarding FOG occurrence (83% in STN-group, 88% in BMT group). All freezers had *off*-FOG and 6 patients in each group also experienced FOG during *on.* No pure *on*-FOG was observed throughout this study. Baseline characteristics did not differ between patients who dropped out of the study and those who completed all three assessments.

Insert Table 1 about here

Baseline characteristics

Freezing of gait occurrence

STN-group: Nine out of 20 freezers in the STN-group still had FOG 6 and 12 months after surgery, of which 5 cases had FOG during *on* and *off* and 4 cases only during *off*. Eight baseline freezers converted to being non-freezers at 6 and 12 months follow-up. Three baseline freezers still demonstrated FOG at the 6 months time mark, but had no FOG after 12 months. Two patients in the STN-group did not have FOG throughout the study period. Finally, two baseline non-freezers converted to being freezers, one case with FOG only during *off* and one with FOG during *on* and *off*.

BMT-group: In the BMT-group, all 15 persons who had FOG at baseline continued to have FOG during follow-up. Moreover, four of the baseline *off*-freezers also developed FOG in *on* after 6 and 12 months. Of the 2 baseline non-freezers, one developed FOG during *on* and *off* at the two follow-up tests resulting in 9 *on*-and-*off*-freezers in the BMT-group after 12 months. One patient showed no freezing at the 3 test moments.

Insert Figure 1 about here

FOG occurrence

Comparison between STN- and BMT-group: First, Fisher Exact Statistics on the primary outcome revealed that at six months follow-up, STN-DBS patients were significantly less likely to demonstrate FOG than the BMT-group (Table 2). STN surgery was associated with a RRR of 0.40 and the number needed to treat was 3 (95% CI, 2 - 10). Similar results were obtained at 1-year post-surgery.

Insert Table 2 about here

FOG occurrence NNT

Second, main and interaction effects of group (STN, BMT) and time (baseline, 6 months, 12 months) on FOG occurrence were investigated via the GEE model. A significant interaction effect was found on the dataset with imputed cases (dropout at 6 months: N=1, at 12 months: N=5) in favour of the STN-group (Wald X^2= 7.86; p = 0.02). Post-hoc comparisons showed that patients in the STN-group were less likely to freeze at 6 month follow-up (mean difference = -2.03; 95% CI (-3.99 – -0.07); p = 0.04) compared with the BMT-group (Figure 1). After adjustment for baseline differences in LED scores, the interaction effect of group*time was no longer significant (Wald X^2 = 1.12; p = 0.57).

The difference in FOG occurrence between groups was more pronounced at 12 months follow-up (mean difference = -2.53; 95% CI (-4.54 – -0.53); p = 0.01). We found a significant within-group reduction in FOG occurrence in the STN- but not in the BMT-group (Wald X^2 = 7.65; p = 0.02). In the STN-group, improvement in FOG occurrence was borderline significant at 6 month follow-up (mean difference = -1.27; 95% CI (-2.57 – 0.02); p = 0.05), and significant at 12 months follow-up (mean difference = -1.78; 95% CI (-3.14 – -0.41); p = 0.01) compared to baseline (Figure 1).

Freezing of gait severity. FOG severity, analysed in freezers only, was significantly different between groups 6 months postoperatively (t = 2.89, p = 0.008), and borderline significant at 12 months (t = 2.06, p = 0.05). Similar to FOG occurrence, the GEE model produced a significant interaction effect of group*time based after imputation of missing data (Wald X^2 = 6.51; p = 0.04). Figure 2 shows the post-hoc comparisons of the GEE model. At six months follow-up, the STN-group reported significantly less FOG severity (34.2% of the baseline score) than the BMT-group (mean difference = -5.89 points on NFOGQ; 95% CI (-9.70 – -2.09); p = 0.03). These differences were maintained at 12 months follow-up (mean difference = -7.05; 95% CI (-11.38 – -2.71); p = 0.02). The interaction effect of group*time was no longer significant when accounted for baseline LED (Wald X^2 = 1.68; p = 0.43).

No within group changes were observed in BMT-group, while the STN-group obtained better NFOGQ total scores at 12 months follow-up (mean difference = -5.70; 95% CI (-9.35 – -2.04); p = 0.03) compared to baseline. There was a trend towards improvement (mean difference = -4.79; 95% CI (-8.30 – -1.28); p = 0.06) in the STN-group from baseline to 6 month follow-up.

Insert Figure 2 about here

FOG severity

Clinical evaluation

Several clinical measures improved at follow-up in the STN- but not in the BMT-group (Table 1). As expected, LED doses were reduced in the STN-group 6 and 12 months post-surgery compared to baseline (63.1 and 61.3% reduction respectively, $p<0.01$) and BMT ($p<0.01$). The distribution of other medication doses remained similar between groups except for amantadine which was more frequently administered in the BMT compared to the STN-group ($p=0.04$) at 12 months (See Supplement 2). Additionally, UPDRS motor scores, on/off fluctuations (UPDRS IVb) and PDQ-39 scores showed significant improvements at 6 and 12 month follow-up compared to baseline ($p<0.01$ for all comparisons), resulting in lower (better) scores than the BMT-group. In the BMT-group, MMSE scores had worsened at 12 months compared to 6 months and baseline assessment ($p=0.02$). No effects on timed gait tests or falls were shown.

Association between improvement in FOG and clinical outcomes following STN-DBS.

We examined which clinical factors predicted the conversion from freezer to non-freezer

Freezer-to-non-freezer conversion at 6 months was marginally correlated with baseline LED

(R=0.45, p=0.05), meaning that freezers with a higher baseline LED had a higher likelihood of converting to being a non-freezer after STN-DBS. There were no significant correlations with the change in other clinical variables, including LED change and other UPDRS IVb. Freezer-to-non-freezer conversion at 12 months was significantly correlated with the relative reduction in LED (expressed as percentage of baseline LED, R=0.46, p=0.04) and with the reduction in on/off fluctuations (UPDRS IVb scores, R=0.47, p=0.03), meaning that freezers with a more pronounced reduction in LED and on/off fluctuations at 12 months follow-up have a higher likelihood to have become a non-freezer at this time point. Other correlations were not significant. To further examine the relative independence of LED-reduction and UPDRS IVb-reduction in explaining the freezer-to-non-freezer conversion, we applied a multivariate logistic regression model including these two factors. In this full model regression analysis, the change in UPDRS IVb scores entered the model first and explained 21% of the variance between 'converters' and 'non-converters' (R^2=0.21, p=0.037). Next, the LED reduction entered the model and proved a secondary, independent factor explaining an additional 20% of variance (R^2=0.20, p=0.026). Jointly, the two factors explained 41% of the variance between 'converters' (N=11) and 'non-converters' (N=9).

DISCUSSION

This is the first prospective, controlled study into the effect of bilateral STN stimulation on self-reported freezing of gait (FOG) as experienced in daily life. The results were in favour of STN-DBS. Following surgical treatment, freezers were more likely to 1) convert to being non-freezers (RRR=0.4) and 2) experience a reduction in FOG severity. These effects were mediated by a reduction in patients' LED and motor fluctuations. Patients who continued BMT showed worsening of FOG symptoms (more *on/off* FOG). In agreement with previous

literature,[6, 7] we found that STN-DBS also led to improved motor symptom severity and quality of life.

As quality of life improvement is a well-established finding,[7] the current study examined the effects of STN-DBS on FOG in a non-randomized way for ethical reasons. This induced a small difference in subject number between groups at baseline. Patients who chose to undergo STN-DBS were comparable to BMT-treated patients at baseline on all clinical parameters, except for their higher LED score. It is noteworthy that this suggests a slightly more severe disease profile in the STN-DBS group, adding strength to the positive treatment outcomes found in this group. We did not assess FOG in a blinded way which is a limitation of the current study.[1] However, the NFOGQ is a validated tool to evaluate FOG occurrence and severity over a period of 1 month rather than in a single test session, which adds to the ecological validity of the findings.[13]

The present study suffered from dropout (N=5) in the control arm due to the natural progression of the disease. We performed a thorough and conservative statistical control for this drawback, through imputation and GEE-modeling. Therefore, it is unlikely that dropout influenced the interpretation of the results.

The mainstay of therapy for FOG is to prolong clinical '*on*' periods.[1] Stimulating the STN does not directly produce striatal dopamine release but may boost the dopamine motor system by inhibiting overexcited STN neurons,[5, 17] reducing the neuronal synchronization in the vicinity of STN, [18] and altering connectivity of thalamocortical pathways.[19] Similarly, methylphenidate, which enhances synaptic dopamine, was recently suggested to improve FOG in combination with levodopa and STN-DBS.[20]. Still, response to STN-DBS in relation to FOG is heterogeneous with pre-surgical levodopa-responsiveness, disease duration and age as best predictors of outcome.[11, 21] An important finding of the present study was that the reduced levodopa dose equivalent and improved motor fluctuations discriminated

between baseline freezers who no longer experienced FOG 12 months after surgery (55%) and those who did (45%). This is in line with a recent multivariate model in which increased LED, over and above its reflection of disease severity, was a significant predictor of FOG.[22] On the other hand, a meta-analysis of long-term effects of DBS of STN and GPi,[23] suggested that the reduced levodopa dosages, enabled by STN-DBS, may be responsible for a quicker reappearance of postural and gait disturbances as compared to GPi-stimulated subjects after 2 years. These findings support the complex relationship between FOG and levodopa, suggesting that FOG is partially levodopa-responsive and partially dependent on other neurotransmitter systems with extremes at both ends of the spectrum.[1, 2]

Our results of post-surgical improvement of FOG severity substantiate recent findings of Niu et al.,[24] who examined a similar follow-up period, but no control group and no freezer to non-freezer conversion. FOG can also emerge after STN stimulation.[11, 25] In our STN-DBS-group 2 of the 4 non-freezers at baseline developed FOG after surgery. Similarly, one of the 2 baseline non-freezers in the BMT group demonstrated FOG at 6 and 12 months follow-up. Emergence of FOG in some patients after STN stimulation may reflect disease progression rather than a side effect of stimulation, although our sample of non-freezers was too small to make firm conclusions. In the BMT-group, disease progression was reflected by the increase from 2 to 6 patients experiencing FOG in both *on* and *off*.

Freezers treated with STN-DBS who had converted to being non-freezers at 12 months follow-up all had stimulation frequencies of 130 Hz (n=11) or more (n=2). This result is interesting in the light of recent studies that suggest controversial results on lowering the stimulation frequency to specifically target axial symptoms and FOG in the short and/or long term.[8, 9, 10, 26, 27]

Clinically, FOG is influenced by a range of motor and non-motor problems which may respond differently to STN-DBS.[1, 22] The central motor component of FOG relates to poor control of timing and scaling of movement which predisposes freezers' locomotor pattern and other repetitive movements to a critical breakdown.[1, 28-30] In the context of freezing during upper limb motion, we recently showed that patients with FOG overactivated the STN, pallidum and putamen while prefrontal motor regions were underactivated compared to non-freezers and controls.[31] As such, freezing-related alterations of brain activity were located within the striatofrontal circuitry which is likely to be influenced by STN-DBS. Positive effects of STN-DBS on stride length,[32] bilateral coordination,[33] symmetry,[32] and turning [34] have been reported and could thus diminish FOG after STN-DBS. However, improvements of timed gait in the STN-group in this study did not reach significance, suggesting a FOG-specific effect of STN-DBS as an alternative explanation. In line with recent neuroimaging studies suggesting a supplementary role of nondopaminergic locomotor circuitries,[35-37] low frequency stimulation of the PPN, may alleviate FOG without necessarily recovering background spatiotemporal gait abnormalities.[38] Moreover, novel DBS approaches that simultaneously modulate gait control networks through STN, SNr and PPN [39, 40] may produce a synergistic effect on FOG.

CONCLUSION

In this prospectively controlled study, STN-DBS alleviated FOG in 55 % of freezers at 6 and 12 months after surgery compared to worsening of FOG when treated with BMT. Freezers treated with STN-DBS were also more likely to experience reduced FOG severity during follow-up compared to patients who stayed on BMT. The improvement of FOG after STN-DBS may be partially driven by the dopamine-reducing effects and reduced on/off

fluctuations. Future follow-up trials are warranted to evaluate if therapeutic benefits persist with disease progression.

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COMPETING INTERESTS STATEMENT

All authors report no conflict of interest.

CONTRIBUTORSHIP STATEMENT

Author contributions:

1) *the design and conceptualization of the study*
2) *analysis and interpretation of the data*
3) *drafting and revising the manuscript*

Sarah Vercruysse: *2 and 3*

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Tables

Table 1 Clinical characteristics of the STN- and BMT-groups at baseline, 6 and 12 months follow-up.

		STN-group (n = 24)			BMT-group (n = 17)			Group comparison		
		T0 Baseline	**T1 6 months**	**T2 12 months**	**T0 Baseline**	**T1 6 months**	**T2 12 months**	**T0**	**T1**	**T2**
Age *(years)*	Mean[a] *(Stdev)*	58.33 *(+/-9.56)*	-	-	58.12 *(+/-6.57)*	-	-	0.94		
Gender *(m/f)*	Freq.[b]	14/10	-	-	8/9	-	-	0.48		
DD *(years)*	Mean[a] *(Stdev)*	11.88 *(+/- 5.10)*	-	-	12.47 *(+/-4.10)*	-	-	0.40		
Freezing *(yes/no)*	Freq.[c]	20/4	14/10[1]	11/13[1]	15/2	16/1	16/1	1.0	**0.01**	**0.01**
H & Y on *(range, 0 – 5)*	Median[d] *(IQR)*	*2.75 (2.00-3.00)*	*2.5 (2.00-3.00)*	*2.5 (2.0-3.0)*	*2.5 (2.0-3.0)*	*2.5 (2.0-3.0)*	*2.5 (2.5-3.0)*	0.82	0.74	0.56
UPDRS III *(range, 0 – 108)*	Mean[a] *(Stdev)*	*31.13 (+/-15.23)*	*22.92**[1]** (+/-8.42)*	*21.38**[1]** (+/-8.93)*	*26.47 (+/- 14.72)*	*30.41 (+/-11.71)*	*31.29 (+/-10.38)*	0.81	0.35	1.0
UPDRS IV *(range, 0 – 23)*	Mean[a] *(Stdev)*	*9.29 (+/-2.94)*	*4.08**[1]** (+/-3.56)*	*3.38**[1]** (+/-2.32)*	*9.24 (+/-1.78)*	*9.47 (+/-2.72)*	*9.71 (+/-1.96)*	1.0	**<0.01**	**<.0.01**
LED*1 *(mg/day)*	Median[d] *(IQR)*	*1112.5 (780-1369.2)*	*410.0**[1]** (208.5-458.3)*	*430.0**[1]** (208.5-557.5)*	*680.0 (515-780)*	*606.6 (515-866.7)*	*615.0 (515-915)*	**<0.01**	**<0.01**	**<0.01**
Falls *(range 0 – 2)*	Median[d] *(IQR)*	*0 (0-1)*	*0 (0-2)*	*0 (0.00-1.25)*	*1 (0-2)*	*0 (0-1)*	*1 (0-2)*	0.12	0.80	0.55
TUG*2 *(seconds)*	Mean[a] *(Stdev)*	*13.09 (+/-9.93)*	*10.90 (+/-2.84)*	*10.81 (+/-4.31)*	*11.53 (+/-3.55)*	*11.79 (+/-3.31)*	*11.49 (2.96)*	0.94	1.0	1.0
MMSE *(range, 0 – 30)*	Median[d] *(IQR)*	*29 (28.75-30)*	*29.50 (28.75-30.00)*	*29 (28-30)*	*30 (29-30)*	*30 (29-30)*	*29**[1,2]** (28-29)*	0.12	0.60	0.31
PDQ-39*3 *(range, 0 – 800)*	Mean[a] *(Stdev)*	*280.69 (+/-116.39)*	*189.94**[1]** (+/-8.63)*	*185.33**[1]** (+/-111.00)*	*341.86 (+/-105.86)*	*332.92 (+/-123.29)*	*315.88 (+/-112.74)*	0.58	**<0.01**	**0.01**

aRepeated measures ANOVA tests with Time (T0, T1, T2) as within-subject and Group (STN, BMT) as between-subject factors were used. Reported p-values are based on Tukey HSD post-hoc comparisons. **b**Chi-square test was used for between-group comparison. **c**GEE model was used (see text). **d**Non-parametric tests were used for between-group comparisons (Wilcoxon rank sum test) and within-group analysis (Friedman test with Wilcoxon paired t-test for post-hoc comparisons) over T0, T1 and T2.

Abbreviations: BMT = best medical treatment; freq.= frequencies; DD= disease duration; H&Y: Hoehn and Yahr; LED = Levodopa Equivalent Dose; TUG= Timed up and go; MMSE = Mini Mental State Examination; PDQ-39 = Parkinson's Disease Quality of Life Questionnaire; STN = subthalamic nucleus; UPDRS = Unified Parkinson's Disease Rating Scale.

1P-value < 0.05 compared to T0. **2**P-value < 0.05 compared to T1.

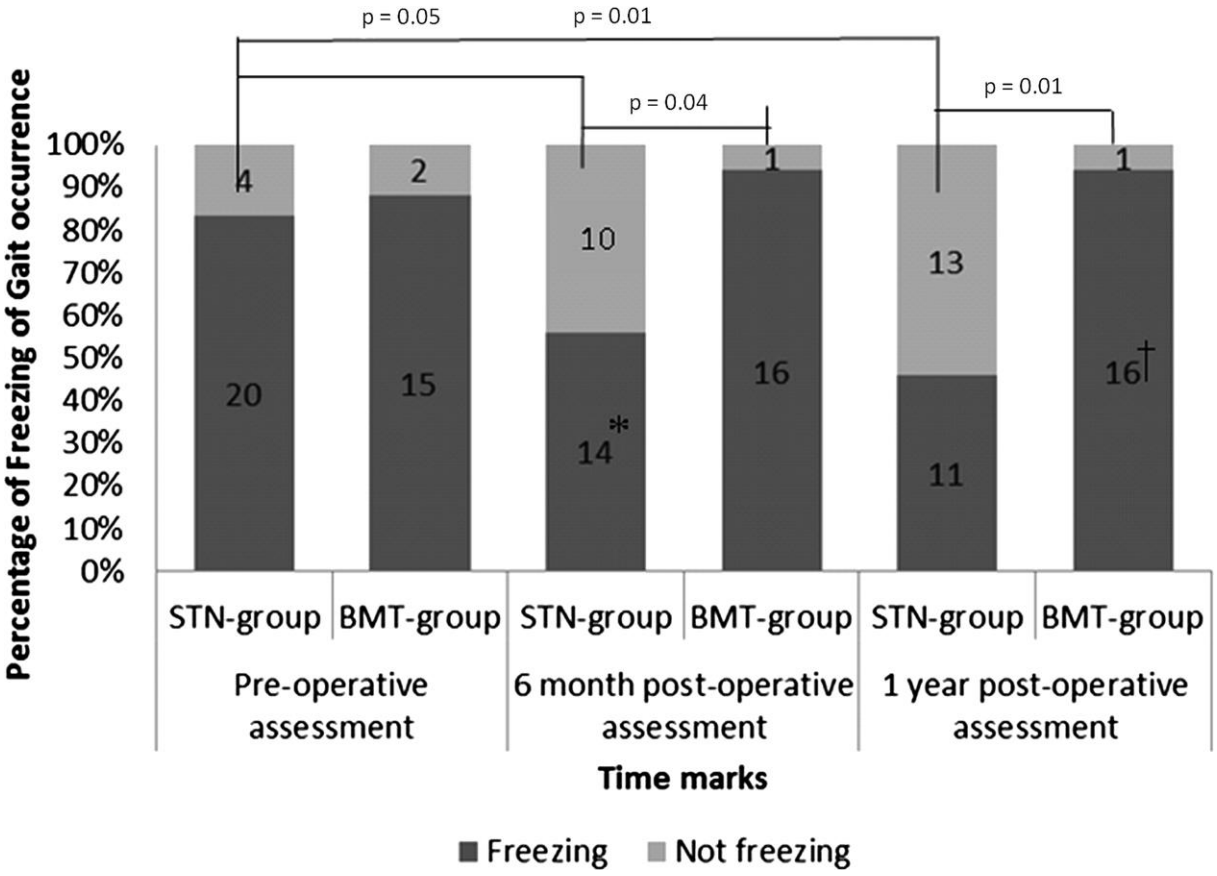
*1: 5 missing LED values in the BMT-group were imputed using LOCF method. Results were similar without imputation. *2: 1 missing TUG score in the BMT-group was imputed using LOCF method. Results were similar without imputation. *3: 1 missing PDQ-39 score in the STN-group was imputed using LOCF method. Results were similar without imputation.

Table 2. Freezing of Gait occurrence at 6 and 12 months follow-up in the STN- and BMT-group

Freezing of Gait	6 months follow-up		12 months follow-up	
	STN-group N = 23	BMT-group N = 17	STN-group N = 24	BMT-group N = 12
Freezing, n (%)	13 (57%)	16 (94%)	11 (46%)	11 (92%)
No freezing, n (%)	10 (43%)	1 (6%)	13 (54%)	1 (8%)
Test statistic, p value	Fisher's Exact, p = 0.01		Fisher's Exact, p = 0.01	
Effect size	1.38		1.41	
Number Needed to Treat	3 (2 – 10)		2 (2 – 8)	
Relative Risk Reduction	0.40 (0.12 – 059)		0.50 (0.20 – 0.69)	

Figure legends

Figure 1. Occurrence of freezing of gait in the STN-group (n = 24) and BMT-group (n = 17) at baseline, 6 and 12 months follow-up.



* FOG occurrence of 1 freezer in the STN-group was imputed at 6 month follow-up.

† FOG occurrence of 5 freezers in the BMT-group was imputed at 12 month follow-up.

Figure 2. Freezing of gait severity in the STN- (n = 11) and BMT-group (n = 15) at baseline, 6 and 12 month follow-up.